S7 – Persistence of Ciguatera Fish Poisoning and its Associated Neurological Manifestations in Mice

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Background: Ciguatera fish poisoning (CFP) is the most prevalent human food poisoning resulting from ingestion of marine fish containing ciguatoxins (CTXs) affecting over 50,000 people worldwide annually. Ciguatera fish can be found in the Pacific Ocean, Indian Ocean and Caribbean regions. Pacific CTX-1 (P-CTX-1) is the most potent known CTXs and the predominant source of CFP in the region of Pacific Ocean account for the majority of neurological symptoms in patients.

Aims and Objectives: We investigated the neurotoxic effect of P-CTX-1 at doses relevant to human exposure on nervous system repair, functional recovery, and neurotransmitter metabolism in mice.

Methods: Primary neuronal cultures and adult mice were exposed to CTX purified from ciguatera fish sourced in the Pacific region. The concentration of P-CTX-1 in major organs was measured by a neuroblastoma cell bioassay. Functional recovery assays, electroencephalography (EEG) and electromyography (EMG) recordings, and immunohistochemistry before and after a peripheral nerve injury (PNI) following P-CTX-1 exposure were performed. High-performance liquid chromatography-tandem mass spectrometry based target metabolomics in combined with mathematical modeling was performed to delineate the underlying mechanism.

Results: P-CTX-1 was detected in mouse brain and peripheral nerve in hours and accumulated for two months after exposure. P-CTX-1 inhibited intrinsic growth capacity of axotomized peripheral neurons by reducing the axonal growth. P-CTX-1 exposure reduced motor function and EEG activity within the first two weeks before returning to baseline levels in mice. However, these pre-exposed animals sustained delayed and irreversible sensory and motor function deficits after PNI where functional synapse formation was impaired which correlated with a reduction of EMG activity in muscle. Delayed functional recovery was observed 4 months after P-CTX-1 exposure in PNI mice. Target metabolomics profiling of neurotransmitters revealed disturbance in the balance between excitatory and inhibitory neurotransmitters and their metabolism in the motor cortex.

Conclusions: Our study provides the first evidence that the persistence of P-CTX-1 in peripheral nerve system reduces the intrinsic growth capacity of peripheral neurons, resulting in delayed functional recovery and irreversible motor deficits after injury. The accumulation of P-CTX-1 in the nervous system is evident which accounts for the persistence of neurological manifestations and relapsing of CFP in patients. Furthermore, identification of major pathways affected by P-CTX-1 intoxication provides new insight into potential biomarker development and therapeutic interventions.

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